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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,165	09/07/2004	Sudhirdas K. Prayaga	Cura 85 CON	6533

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,165	PRAYAGA ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 07 September 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's preliminary amendment and sequence listing in both paper form and CRF filed on 9/7/04 have been entered. Claims 1-14 are currently pending and under examination in the instant application. An action on the merits follows.

Priority

Applicant's claim for benefit of priority to parent application 09/689,486 is acknowledged. However, it is noted that this application has issued as U.S. Patent No. 6,855,806 on 2/15/06. Applicant is required to update the status of the parent application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The applicant's claims broadly recite nucleic acid sequences encoding a polypeptide comprising an amino acid sequence selected from a group including SEQ ID NO:5, variants of the amino acid sequence of SEQ ID NO:5 which are at least 96% identical to SEQ ID NO:5, naturally occurring allelic variants of SEQ ID NO:5, and fragments of any of the above. The claims further recite complements of the claimed nucleic acid sequences.

The specification does not provide a sufficient written description for the genus of polypeptides encompassed by these claims or the genus of nucleic acids encoding these polypeptides. The specification discloses a single isolated cDNA, SEQ ID NO:4, which comprises a putative open reading frames encoding a polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:5. The specification further discloses that SEQ ID NO:5 is identical to a partial sequence previously reported as the human EphA8 ephrin receptor, and is 95% identical to the murine ephrin type-A receptor 8 precursor. However, neither the specification nor the art at the time of filing teaches that naturally occurring allelic nucleic acid or polypeptide variants exist for any of the known ephrin receptors. The specification further fails to provide any description as to the nucleic acid or amino acid sequence of any naturally occurring allelic variant of the putative human EphA8 protein, or provide any guidance as to the structural and/or functional characteristics of any such variant. In addition, it is noted that aside from the murine and chick EphA8 receptor, neither the specification nor the prior art teaches that species homologues for the EphA8 receptor exist for other mammalian or animal species or were known at the time of filing.

Further, in regards to other variant nucleic acid sequences encoding at least a portion of a polypeptide comprising an amino acid sequence consisting of SEQ ID NO:5 or a variant thereof

at least 96% identical to SEQ ID NO:5, it is noted that the claims read on any sequence which encodes a polypeptide which comprises any size portion of the amino acid sequence or SEQ ID NO:5 or a variant thereof. As such, the genus of nucleic acids encompassed is enormous, reading on any sequence encoding a polypeptide with essentially 2 or more amino acids in common with SEQ ID NO:5. The specification provides no guidance for the scope of polypeptides or nucleic acids encoding these polypeptides. As noted above, the specification is limited to the disclosure of the murine, chick, and putative human Eph8 receptor polypeptide sequences and provides a single nucleic acid sequence encoding the putative human Eph8 receptor.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304,

312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The applicant has not provided any description or reduction to practice of the breadth of nucleic acid sequences encompassed by the claims, including the universe of nucleic acid sequences which encode a polypeptide comprising any size portion of SEQ ID NO:5, or naturally occurring nucleic acid or polypeptide allelic variants of any of these polypeptides. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides or nucleic acids encoding these polypeptides.. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Thus, for the reasons outlined above, claims 1-14 do not meet the requirements for written description under 35 U.S.C. 112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses nucleic acid sequences encoding a polypeptide comprising an amino acid sequence selected from a group including SEQ ID NO:5, variants of the amino acid sequence of SEQ ID NO:5 which are at least 96% identical to SEQ ID NO:5, naturally occurring allelic variants of SEQ ID NO:5, and fragments of any of the above. The specification further discloses variant nucleic acid sequences encoding at least a portion of a polypeptide comprising an amino acid sequence consisting of SEQ ID NO:5 or a variant thereof at least 96% identical to SEQ ID NO:5. In addition, the specification discloses The claims complements of the claimed nucleic acid sequences, pharmaceutical compositions comprising the disclosed nucleic acids and methods of treating a NOV-associated disease or a pathological condition using the disclosed pharmaceutical compositions or nucleic acids.

As noted above, the specification fails to provide sufficient guidance as to the structural and biological properties of any naturally occurring variant of the putative human EphA8 protein, or provide guidance as to the structural, physical, or biological characteristics of nucleic acids encoding polypeptides which comprises any size portion of the amino acid sequence or SEQ ID NO:5 or a variant thereof.

The specification further fails to identify amino acid residues of SEQ ID NO:5 or nucleic acid sequences of SEQ ID NO:4 which are either crucial or non-essential for the biological activity of the putative human EphA8 protein such that the skilled artisan could predict without undue experimentation which amino acids or nucleotides could be altered without affecting protein folding, stability, and biological activity. While the specification notes the high degree of sequence similarity between the putative human EphA8 protein referred to as NOV2 by the specification and murine EphA8, and provides a working examples demonstrating the expression

of a 64kD protein in cells transfected with an expression vector comprising SEQ ID NO:4, the specification fails to provide any specific guidance as to the particular biological activity of the protein encoded by SEQ ID NO:4, which is alleged to be the amino acid sequence of SEQ ID NO:5. While the art at the time of filing teaches that ephrin receptors are generally tyrosine kinase receptors involved in development, including neuronal development, the specification provides no evidence that the polypeptide encoded by SEQ ID NO:4, or the amino acid sequence of SEQ ID NO:5 is capable of tyrosine kinase activity, capable of binding to any ligand including ephrin, or capable of affecting any type of developmental process. In addition, while the specification provides a working example which describes the detection of mRNA derived from the sequence of SEQ ID NO:4 in various normal and malignant tissues, particularly prostate cancer cell lines, the specification fails to demonstrate actual protein expression of NOV2 (EphA8) in normal or malignant cells or correlate NOV2 (EphA8) expression with any effect on cell growth or tumorigenesis either *in vitro* or *in vivo*.

In addition, the specification fails to provide any guidance as to "NOV-associated" disorders. Based on the known activities of ephrin receptors in development, the specification hypothesizes that NOV2 would be useful for treating neurological, cardiac and vascular pathologies. However, it is noted that neither the prior art nor the specification actually identifies any pathology or disease which is directly affected by the expression or lack or expression of any ephrin receptor. Further, while the specification does observe increased levels of NOV2 mRNA is certain cancer cell lines, the specification fails to correlate the overexpression of NOV2 with the process of tumorigenesis. The specification also fails to provide any guidance for treating cancer using a NOV2 polypeptide or nucleic acid encoding a NOV2 polypeptide. The

specification does not provide any guidance as to the properties or activities of the NOV2 polypeptide that would suggest that the addition of NOV2 polypeptide to cancer cells which already overexpress NOV2 mRNA would result in any effect on cancer growth or metastasis. The applicant is reminded that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) . In the absence of specific information as to the actual biological properties of NOV2 and the identity of diseases or conditions which are directly attributable to NOV2 expression or lack of expression, it would have required undue experimentation for the skilled artisan to identify NOV2 associated diseases.

Furthermore, in regards to the administration of nucleic acids *in vivo*, at the time of filing *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2- see IDS). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1, see IDS). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively

demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2-see IDS BI-1). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the identity of the promoter used to drive gene expression. Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Therefore, in view of the art recognized unpredictability in treating disease by administering nucleic acids at the time of filing, the absence of specific information as to the actual biological properties of NOV2, the lack of guidance concerning the identity of diseases or conditions which are directly attributable to NOV2 expression or lack of expression, the lack of working examples demonstrating any therapeutic effect on any disease or pathology following the administration of a nucleic acid encoding a NOV2 polypeptide, and the breath of the claims, it would have required undue experimentation for the skilled artisan to treat any and all pathological conditions including cancer by administering a nucleic acid encoding a NOV2 polypeptide.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group consisting of....". While group members (a)-(d) recite various amino acid sequences, members (e) and (f) recite nucleic acid fragments or molecules, not amino acid sequences. Therefore, (e) and (f) do not meet the claim limitations for the group, i.e. (e) and (f) are not amino acid sequences. Thus, the claim is confusing and indefinite. In addition, (f) recites a nucleic acid comprising the complement of (a)-(d). (a)-(d) are amino acid sequences, it is unclear what constitutes a "complement" of an amino acid sequence. It is also noted that the complement of a nucleic acid sequence which encodes a polypeptide is a non-coding strand. Therefore, the complement of (e) would not meet the initial limitation of the claim, that the nucleic acid encodes a polypeptide. Thus, the metes and bounds of the claim cannot be determined. Claims 2-14 depend on claim 1 and are therefore included in this rejection.

Claim 6 is further confusing in the recitation that the nucleic acid molecule hybridizes to either SEQ ID NO:4 or its complement. As noted above, claim 1 requires that the isolated nucleic acid molecule encode a polypeptide, therefore nucleic acid sequences which hybridize to the coding strand and thus are non-coding do not meet this limitation. Furthermore, the metes and bounds of "stringent hybridization" are unclear. The specification does not provide a specific definition for "stringent hybridization". Pages 29-30 disclose that, "stringent conditions are sequence-dependent and will be different in different circumstances", and that "stringent

conditions" are known in the art. The specification on page 30 also gives on non-limiting example of a stringent hybridization condition. However, based on the disclosure that "stringent conditions" vary based on the sequence, the metes and bounds of what constitutes a stringent condition cannot be determined.

Claim 7 is further confusing in that the recited group of nucleic acid molecules includes a first nucleic acid sequence and a second isolated polynucleotide. It is unclear from the claim language whether the applicant intends to claim a single nucleic acid molecule or a composition of a first isolated nucleic acid molecule according to claim 1 and a second isolated polynucleotide. Further, in (a) it is unclear which amino acid is being referred to as "said amino acid sequence" as claim 1 recites several different amino acid sequences. Also, in (b) it is unclear which coding sequence is being referred to as "said coding sequence" as two different coding sequences are recited in the claim. In addition, regarding the complement, it is again noted that claim 1 recites a nucleic acid sequence that encodes a polypeptide. Therefore, the claim does not encompass non-coding sequences. Claims 8 and 9 depend on claim 7 and thus are included in this rejection.

Claim 14 provides for the use of the nucleic acid of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 14 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e.,

results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Chan et al. (1991) Oncogene, Vol. 6 (6), 1057-1061. The applicant claims an isolated nucleic acid sequence comprising a polypeptide comprising a fragment of an amino acid sequence as set forth in SEQ ID NO:5. Chan et al. teaches a human EEK cDNA which encodes a polypeptide with an amino acid sequence that is 100% identical to a fragment of SEQ ID NO: 5. Further, the cDNA is no more than 20% different from the nucleic acid sequence of SEQ ID NO:4. Thus, by teaching all the limitations of the claims as written, Chan et al. anticipates the instant claims.

Claims 1 and 5-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Park et al. (1997) Oncogene, Vol. 14, 533-542. The applicant claims an isolated nucleic acid sequence comprising a polypeptide comprising a fragment of an amino acid sequence as set forth in SEQ

ID NO:5 or a variant of said sequence which is 96% identical to SEQ ID NO:5, and a vector comprising said nucleic acid operably linked to a promoter. Park et al. teaches a full length cDNA encoding mouse EEK and an expression vector comprising the EEK cDNA operably linked to a promoter (Park et al., page 540). While the entire amino acid sequence of mouse EEK is approximately 95% identical to that of SEQ ID NO:5, portions of the sequence are at least 96% identical. As such, the mouse sequence meets the claim limitation for nucleic acid encoding a polypeptide comprising a fragment of a polypeptide which is 96% identical to SEQ ID NO:5. Further, as the mouse cDNA has greater than 80% sequence homology to SEQ ID NO:5, the cDNA disclosed by Park further meets the limitation that the coding sequence differs by no more than 20% from the coding sequence of SEQ ID NO:5. Thus, by teaching all the limitations of the claims as written, Park et al. anticipates the instant invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER